BIOCOMPATIBLE

1.	*Abbott Xience PMA Module 2* at § 3.2.P.2. (ABT310762) ("At predevelopment stage, polymers were screened by the following criteria: . . . vascular biocompatibility . . . Two polymers, poly (n-butyl methacrylate) (PBMA) and poly (vinylidene fluoride co-hexafluoropropylene) (PVDF-HFP) passed the initial screen and were selected for further evaluation.").
2.	*Xience PMA Panel Meeting Tran.*, at p. 50 (CORD114741) ("[The drug-carrying matrix on Xience V] is one of the most stable entities chemically because of its durable carbon carbon backbone and the covalent carbon fluorine bonds. And this stability confers to this polymer a high degree of stability in vivo as well as biocompatibility. And, finally, this polymer has good hemocompatibility.").
3.	*Xience PMA Panel Meeting Tran.*, at p. 52 (CORD114743) ("We have also developed a thin, biocompatible drug coating that is effective at low drug loading").
4.	*Xience PMA Panel Meeting Tran.*, at p. 53 (CORD114744) ("The biocompatibility of the XIENCE V system was demonstrated through numerous in vitro and in vivo studies.").
5.	*Xience PMA Panel Meeting Tran.*, at p. 136 (CORD114827) ("Dr. Simhambhatla presented to you the overview of the XIENCE V design. . . . It has a thin biocompatible drug coating. . . .The long-term biocompatibility is similar to a VISION bare metal stent.").
6.	*Abbott Xience PMA Amendment*, at p. 6-42; 6-48 (ABT0372498) ("Biocompabitility studies on Xience V EECSS demonstrated that the product conformed to the requirements of ISO 10993 and USP<87/88> where applicable."; "The test data generated to date from lot release and additional characterization tests, demonstrate that the quality of the PVDF-HFP material, a critical component in Xience V coating solution is adequately controlled. . . . The identity, mechanical properties, manufacturability, purity and biocompatibility of the polymer have been demonstrated.").
7.	*Xience V/Promus EECSS Risk Assessment Report* at § 5.1.1 (ABT507101) ("A series of short-term biocompatibility tests were conducted in compliance with Good Laboratory Practices (GLP) regulations to demonstrate that the materials and components of the Xience V Everolimus Eluting Coronary Stent System (EECSS) are biocompatible.").
8.	*FDA Panel Meeting re: Late Stent Thrombosis and DES Master Response Document* at p. 1 (ABT1296665) ("Each element of the Xience system contributes to healthy, complete healing: . . . Polymer coating: ultra-thin, biocompatible fluoropolymer with excellent integrity designed for safety and efficacy.").
9.	*XIENCE V Training: Polymer* at p. 6 (ABT1309570) ("XIENCE V Polymer Coating: Type of Polymer: Acrylic and Fluorinated; Biocompatible")
10.	*TCT 2005 Thursday-Friday/October 20-21, 2005 Update* at p. 1 (ABT0951353) ("[Gregg] Stone described the polymer in great detail-it is an acrylic and fluorinated polymer, 'described as inert,' 'biocompatible,' 'easy to manufacture,' 'non-tacky,' and 'has good mechanical integrity.'").

11.	*E-mail from Kay Myrdal, Director of Sales, Abbott, to Murthy Simhambhatla, Manager, Materials Science, Abbott, re key Xience positioning messages* at p. 1 (ABT1285030) ("XIENCE V achieves VISIONARY PERFORMANCE by taking VISION, the proven MULTI-LINK platform, to VISIONARY with the integration of the state-of-the-art drug Everolimus and biocompatible polymer.").
12.	*Letter from Richelle Faria, Guidant Regulatory Affairs Associate, to Center for Devices and Radiological Health* at p. 1-9 (ABT0227295) ("The safety and biocompatibility of acrylic and fluoro deposited polymer coatings have been demonstrated based up the Xience V EECSS biocompatibility testing per ISO 10993-1 and the long use of these polymers in medical implants.").
13.	*E-mail from Murthy Simhambhatla, Manager, Materials Science, Abbott, to Frank von Arx, Head of Project Management TX & I, Novartis, re Studies linking drug-eluting stents to increased mortality/MI spark impassioned pleas for reason and calls for calim* at p. 1 (ABT1343046) ("Our view is that Xience, a 2nd generation DES is safe and efficacious as demonstrated by the SPIRIT II clinical data. Our design paradigm with thin struts, biocompatible polymers, and good coating integrity, together with very compelling pre-clinical results related to inflammation and thrombus burden relative to metallic stents bode well for this system as we continue to gather clinical data on Xience V.").
14.	*Press Release, Abbott, Abbott Begins Early International Launch of Xience V Everolimus Eluting Coronary Stent System*, at p. 2 (ABT1045339) ("Its highly deliverable MULTI-LINK VISION coronary stent platform, the biocompatible coating and the anti-proliferative, anti-inflammatory, everolimus, plus encouraging clinical results, suggest that Xience V will become a preferred treatment choice for coronary artery disease in Europe.").
15.	*Clinical, Angiographic, and IVUS Results from the Pivotal U.S. Randomized SPIRIT III Trial of the XIENCE V Everolimus Eluting Coronary Stent System*, at p. 3 (ABT1098587) ("The XIENCE V DES elutes everolimus from a thin (7.8 μm), robust, durable biocompatible fluoropolymer, incorporating thin cobalt chromium stent struts (0.0032") for enhanced flexibility and deliverability.").

3.2.P.2 PHARMACEUTICAL DEVELOPMENT

This section provides information on the pharmaceutical development of the XIENCE™ V Everolimus Eluting Coronary Stent System. It includes developmental information and studies conducted to establish the commercial dosage of the drug product, formulation, manufacturing processes, critical process controls, microbial attributes, and usage instructions. Relevant sections of ICH Q6A and Q6B were considered as part of the development process.

A glossary of terms is provided for ease of reference and intended context. Due to the amount of information and variation of topics in this section, a table of contents is also included.

3.2.P.2.1 Components of the Drug Product

The following sections provide background information on the development of the coating for the stent implant of the XIENCE™ V Everolimus Eluting Coronary Stent System. The screening of polymers, compatibility between polymers and drug substance, and the selection process for the drug product design and composition are discussed. No changes were made to the quantitative formulation after the start of the SPIRIT II and III clinical trials.

3.2.P.2.1.1 Drug Substance

Everolimus is the active pharmaceutical ingredient used in the manufacture of XIENCE™ V EECSS by Abbott Vascular. Novartis Pharma AG manufactures everolimus in Basel, Switzerland and supplies the drug substance to Abbott Vascular. Novartis manufactures and distributes Certican® (everolimus) tablets for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving an allogeneic renal or cardiac transplant. Certican® has been approved in more than 60 countries outside the U.S. Reference Novartis NDA numbers: 21-560 and 21-628. Novartis has received two approvable letters for Certican® from the FDA. A letter from Novartis Pharmaceuticals Corporation authorizing FDA to reference relevant sections of the Certican® IND and NDAs is provided in Section 1.0 General Information. Drug substance and polymer compatibility is discussed later in 3.2.P.2.1.2 Excipients.

Biological Properties

Everolimus is a potent anti-proliferative agent acting on a wide range of cell types, including vascular smooth muscle cells, which it inhibits at the low nanomolar level (IC_{50} = 0.9 – 3.6 nM).[1] Proliferation of vascular smooth muscle cells is generally regarded as a major factor in the development of restenosis. The combination of inhibition of smooth

[1] Schuler, W. et al. SDZ-RAD, a new rapamycin derivative, Transplantation, Vol. 64, 36-42, 1997.

muscle cell proliferation and relatively high potency makes the drug an attractive candidate for extended delivery from the coating on a drug eluting stent for the prevention of restenosis.

Physical Properties

Everolimus is a lipophilic compound with a low solubility in water (< 0.01 % w/w) and the octanol:water partition coefficient is approximately 10^4. Reference Table 3.2.P.2-1 for solubility of everolimus in a wide range of solvents, including ethanol, acetone, ethylacetate and cyclohexanone. The solubility in organic solvents facilitates the selection of suitable solvent systems to apply the drug to the stent. The solubility of the drug in a number of solvents relevant to the development program is listed below.

The molecular weight of everolimus (958.25) is sufficiently high that a low diffusion coefficient in semi-crystalline polymeric matrices (~ 10^{-9} cm^2/sec) can be expected, which limits the rate at which the drug is released from a polymeric formulation.[2] The dissolution rate from the matrix is further limited by the low solubility of the drug in water, which also virtually prevents any osmotic contribution to polymer swelling. This combination of physical properties supports the suitability of this drug for extended delivery from a polymer matrix of limited thickness.

[2] Controlled Release of Biologically Active Agents, Baker, R. Wiley-Interscience, 29-33.

Table 3.2.P.2-1 Solubility of Everolimus
Data are from Novartis unless specified.

Solvent	Solubility % m/V (g/100 mL solution)	Description Term [2]
Acetone	> 10%	Fs
Acetonitrile	> 10%	Fs
Cyclohexanone [1]	> 10%	Fs
Dimethyl acetamide [1]	>10%	Fs
Ethanol	> 10%	Fs
Ethanol 95 %	> 10%	Fs
Ethyl acetate	> 10%	Fs
Isopropyl acetate	> 10%	Fs
Isopropyl alcohol	> 10%	Fs
Methanol	> 10%	Fs
n-heptane	0.05%	Vsls
n-Octanol	> 10%	Fs
Propylene glycol	> 10%	Fs
Tetrahydrofuran [1]	>10%	Fs
Xylene [1]	> 10%	Fs
Water	< 0.01%	Ins
Acetonitrile / water 53 : 47 (w/w)	> 10%	Fs
Buffer citrate (Titrisol MERCK) pH 6.0	< 0.01%	Ins
Buffer citrate (Titrisol MERCK) pH 8.0	< 0.01%	Ins
Sodium chloride 0.9% in water	< 0.01%	Ins

1. Data obtained at Abbott Vascular.
2. Per USP, Fs: Freely soluble, Ins: Insoluble, Sls: Slightly soluble, Vsls: Very slightly soluble, Sps: Sparingly soluble

Chemical Properties and Stability of Drug Substance
Detailed chemical and physical properties of everolimus drug substance are documented in Novartis' Report RAD 001-Stabilize with BHT (Everolimus Drug Substance), AP3015534A. Properties relevant to Abbott Vascular's application are summarized below.

1. Acid conditions: Strongly acidic conditions will subject the drug substance to hydrolytic and oxidative degradation.
2. Basic conditions: Strongly basic conditions will subject the drug substance to hydrolytic degradation.
3. Temperature / Oxidation: The everolimus drug substance is sensitive to temperature and the combination of air (oxidants) and temperature. The drug substance is formulated with 0.2% BHT as a stabilizer.

4. Light sensitivity: Direct sunlight degrades the drug, while indirect day light does not if the exposure is not more than several hours.

For the drug product, forced degradation studies under exposure to acid, base, temperature and light were performed as part of the impurity assay development and validation and are documented in section 3.2.P.5.3 Validation of Analytical Procedures: Validation Summaries for Degradation Products, Method and Total Content Method.

The compatibility of the drug substance with the excipients in the formulations was found to be acceptable, and is detailed in Section 3.2.P.2.1.2 Excipients.

This combination of chemical properties forms the basis for the suitability of the drug substance for the manufacturing process and composition of the drug product. For further characterization, Table 3.2.P.2-2 provides additional physicochemical properties from Novartis' NDA No. 21-560 Certican® (everolimus) Tablet and NDA No. 21-628 Certican® (everolimus) Tablet.

Table 3.2.P.2-2 Physicochemical Properties

Drug glass transition	~85°C
Distribution coefficients	P (octanol:water) = 10^4
pH value	Range from pH 4 to pH 6 (0.1% suspension in 1% aqueous solution of KNO_3)
PKa value	Neutral compound
Specific optical rotation	-149.4°
Hygroscopicity	Slightly hygroscopic (0.61% increase after 1 week at 25°C/75% RH)
Physical form	Amorphous solid

3.2.P.2.1.2 Excipients

The XIENCE™ V Everolimus Eluting Coronary Stent System has a drug eluting coating consisting of two layers, a primer layer and a drug matrix layer. The primer and the drug matrix layers are applied to the stent from a solution of the polymer in acetone and cyclohexanone. These solvents are removed to acceptable levels (≤ 2 µg/stent) as part of the overall manufacturing process.

Compressed nitrogen is used as the propellant in the atomization process and is considered a processing aid. The nitrogen is industrial grade with a minimum purity level of 99.998%. Ethanol, which is 190 proof USP grade, is used for washing the PBMA polymer that comprises the primer coating. The ethanol is removed during the purification process as indicated by analytical solvent testing to acceptable levels per ICH

guidance on residual solvents.[3] The excipients listed in Table 3.2.P.2-3 below have been demonstrated to function as intended throughout product manufacture and product shelf life. The process followed for their selection is described in more detail below.

Table 3.2.P.2-3 Formulation of the Primer Layer

Constituents	Classification	Function
PBMA poly (n-butyl methacrylate)	Non-compendial	Primer layer Provides adhesion between stent surface and drug matrix
Acetone	NF/EP	Rapidly evaporating solvent component. Provides optimal viscosity for spray coating and evaporates fast enough to prevent coating sagging and webbing.
Cyclohexanone	ACS	Slowly evaporating solvent component. Evaporates slowly in order for coating to maintain fluidity long enough to optimize film formation and adhesion.

Table 3.2.P.2-4 Formulation of the Drug Layer

Constituents	Classification	Function
PVDF-HFP copolymer of poly (vinylidene fluoride and hexafluoropro-pylene)	Non-compendial	Matrix polymer used to • Localize drug on the stent • Provide controlled release of drug after implantation • Maintain coating integrity and adhesion • Provide biocompatible surface
Everolimus	Drug	Anti-proliferative drug to inhibit restenosis
Acetone	NF/EP	Rapidly evaporating solvent component. Provides optimal viscosity for spray coating and evaporates fast enough to prevent coating sagging and webbing.
Cyclohexanone	ACS	Slowly evaporating solvent component. Evaporates slowly in order for coating to maintain fluidity long enough to optimize film formation and adhesion to primer layer.

[3] ICH Harmonised Tripartite Guideline - Q3C Impurities: Guideline for Residual Solvents, July 1997.

Polymer Screening and Selection
At the predevelopment stage, polymers were screened based on the following considerations:

- History of use in implantable devices
- Vascular biocompatibility
- Compatibility with the drug substance
- Coating integrity on the stent
- Coating adhesion to the stent
- Solubility
- Compatibility with spray coating
- Stability, *in vitro* and *in vivo*
- Drug permeability
- Compatibility with sterilization
- Purity

Two polymers, poly (n-butyl methacrylate) (PBMA) and poly (vinylidene fluoride co-hexafluoropropylene) (PVDF-HFP), passed the initial screening and were selected for further evaluation.

PBMA
PBMA is used as an adhesion primer, and is a novel excipient described in detail in section 3.2.A.3 PBMA. Safety information is provided in section 3.2.P.4.6, Novel Excipients. The polymer has no known pharmacological activity. PBMA is also a component of the Cypher® sirolimus-eluting coronary stent, approved under P020026.

PBMA is a flexible methacrylate homopolymer and has an all-carbon backbone composed of alternating secondary and quaternary carbons, which prevents free-radical induced degradation *in vivo*. The steric hindrance from the bulky n-butyl side chain reduces the sensitivity of the ester group to hydrolysis. As a result of these factors, PBMA possesses a high degree of chemical inertness (refer to section 3.2.A.3.S.1.2 for PBMA structure). PBMA has a high affinity to the metal surface of the bare stent, forming a strong anchor. These properties make PBMA a suitable substance to use as a primer on the bare metal stent.

PVDF-HFP
The PVDF-HFP used in XIENCE™ V functions as the drug matrix layer, and is a novel excipient described in detail in section 3.2.A.3. Safety information is provided in section 3.2.P.4.6, Novel Excipients. The polymer has no known pharmacological activity. PVDF-HFP is a component of the PRONOVA surgical (cardiac) suture, which is approved under N16374.

PVDF-HFP is a random copolymer composed of vinylidene fluoride (VDF) and hexafluoropropylene (HFP) monomers. The polymer has a backbone entirely composed of carbon atoms, with 54% of the backbone carbons bearing fluoro or trifluoromethyl groups, and the remaining 46% of the carbons bearing hydrogen atoms. The high dissociation energy of the C-F bonds and the polymer backbone confer a high level of chemical stability to PVDF-HFP. The absence of reactive or enzymatically sensitive groups, such as anhydride, ester, amide, ether, ketone, aldehyde, carbonate, or phosphate bonds makes the polymer resistant to hydrolytic, oxidative, or enzymatic cleavage. (Refer to section 3.2.A.3 for PVDF-HFP structure.)

PVDF-HFP is a semi-crystalline polymer that possesses elastomeric properties. This combination provides the material with the desirable combination of strength (due to the crystallinity) to withstand the mechanical stresses of the manufacturing and clinical use processes, as well as the flexibility and elongation (due to the elastomeric nature) necessary to avoid coating cracks during manufacturing and during implantation and final expansion.

Drug-Polymer Compatibility

The inert nature of the PVDF-HFP and PBMA polymers makes chemical interactions of the drug with either polymer unlikely. To confirm the absence of such interactions, a series of studies were conducted. The compatibility of the drug with the polymers in the coating was evaluated using three analytical techniques: gel permeation chromatography, Raman spectroscopy, and ^{1}H NMR.

Table 3.2.P.2-5 Methods and Findings from Drug and Polymer Compatibility Studies

Method	Detection Principle	Sensitivity	Result
GPC	Detection of drug ultraviolet signal in polymer after physical separation of coating components	0.02 – 0.05% of drug in polymer	No drug detected in polymer fraction
Raman	Detection of changes in infrared absorption of drug and polymer due to chemical interaction between the two	5% change in either drug or polymer	No changes detected
^{1}H NMR	Detection of changes in the chemical environment of protons of drug and polymer indicative of an interaction between the two	2% change in either drug or polymer	No changes detected

In conclusion, no signs of chemical interaction between the drug and either polymer were observed with any of the methods used.

Gel Permeation Chromatography (GPC)

In early research a GPC study was conducted to determine whether the drug substance would bind to either of the polymer excipients. GPC allows separation of the polymer excipients from the everolimus. The non-chromophoric polymers could only be detected by a refractive index (RI) detector. The everolimus could be detected by RI or UV absorbance at 277 nm. Any drug bound to the polymer would cause a UV signal to be detected in the eluting fraction containing the polymer.

During XIENCE™ V manufacture (see section 3.2.P.3), the sterilization cycle exposes the drug product to several hours of elevated temperature. This was used to create a "worst case" scenario. Drug product was subjected to zero, one, two and five sterilization cycles (cycle 15). The samples for analysis were prepared by dissolving the stent coating in tetrahydrofuran (THF) and then analyzed by a GPC column (Waters Styragel® HR 7.8 x 300 mm GPC column) equipped with a refractive index detector, and a UV detector mounted in series. The total drug concentration after dissolving the coating was approximately 600 µg/mL. The detection limit of the triene chromophore is in the 0.1 – 0.3 µg/mL range, or 0.02 – 0.05% of the free drug.

Figure 3.2.P.2-1 shows the chromatogram obtained using refractive index detection of stent samples that were subjected to up to 5 cycles of EtO sterilization. The combined peak of the two polymer excipients can be seen between 14 and 20 minutes, while the large drug peak appears between 25 and 26.5 minutes. The small peak centered around 24.25 minutes is the trace of two aggregated drug molecules. Note that the polymer excipients have a positive and negative peak due to the relative differences in refractive indices between the two polymers and THF.

At the retention time where both polymers were eluted (14-20 min), no UV signal at 277 nm was detected, as is seen in Figure 3.2.P.2–2. This indicates that no drug co-eluted with polymer regardless of the sterilization status or number of sterilization cycles. Mass balance calculations confirmed that the everolimus was recovered in the drug and aggregate peaks. Hence, no drug was bound to either of the polymer excipients.

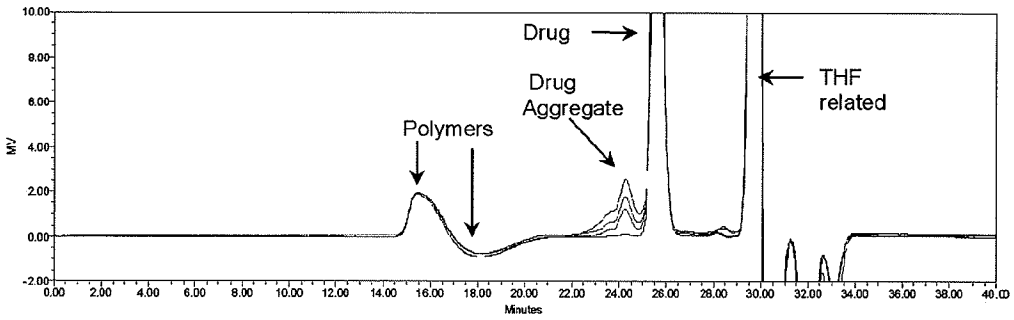

Figure 3.2.P.2-1 Stent Coating Dissolved in THF, Refractive Index Detector
Color code: Red = non sterile, Blue = EtO sterilized (1 cycle), Black = EtO sterilized (2 cycles); Green = EtO sterilized (5 cycles). All EtO sterilization per the original parameters, Cycle 15.

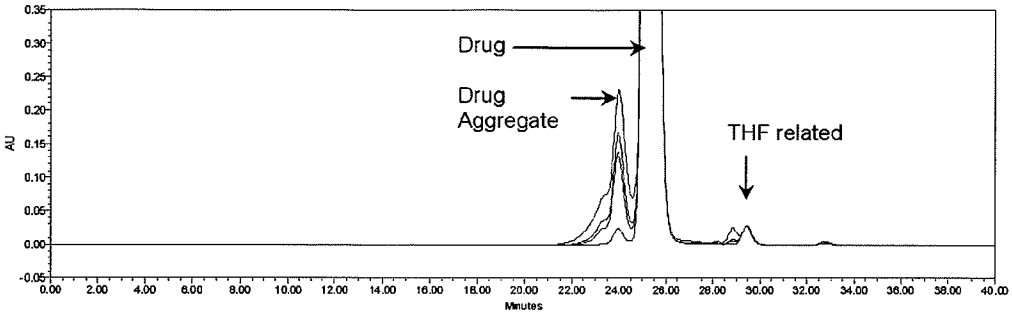

Figure 3.2.P.2-2 Stent Coating Dissolved in THF, UV Detector (277 nm)

Color code: Red = non sterile, Blue = EtO sterilized (1 cycle), Black = EtO sterilized (2 cycles); Green = EtO sterilized (5 cycles). All EtO sterilization per the original parameters, Cycle 15.

In conclusion, there was no evidence of drug substance interaction with either of the polymer excipients when manufactured using the current manufacturing conditions and extreme EtO sterilization processing.

Raman Spectroscopy

Raman spectra were collected for samples of everolimus drug powder, and coated stent samples consisting of polymer-only coated stents (PBMA and PVDF-HFP), and XIENCE™ V stents. The goal of this research study was to detect any spectral changes in the drug or the polymer excipients that would suggest an interaction between the two. The spectra were obtained by using a laser confocal Raman spectrometer (Jobin Yvon HORIBA LabRam HR800) with a CCD detector capable of achieving a 1 μm spatial resolution. Scan times of 10 seconds covered a frequency range of 200-2000 cm^{-1}. Raman spectra were obtained by focusing the laser directly on the stent samples or the coating layer of stents and scanning directly. For stent coatings (XIENCE™ V and polymer-only), three spectra from different locations were taken from all three samples of each stent coating. All coating spectra were scaled using the PVDF-HFP peak at 797 cm^{-1}. The average spectrum, calculated from the nine scaled spectra for each coating type, is presented in Figure 3.2.P.2–3. The everolimus spectrum was measured on the powder form of the drug. It is estimated that a change of 5 wt % of the polymer excipients or the drug product would be detected by this method.

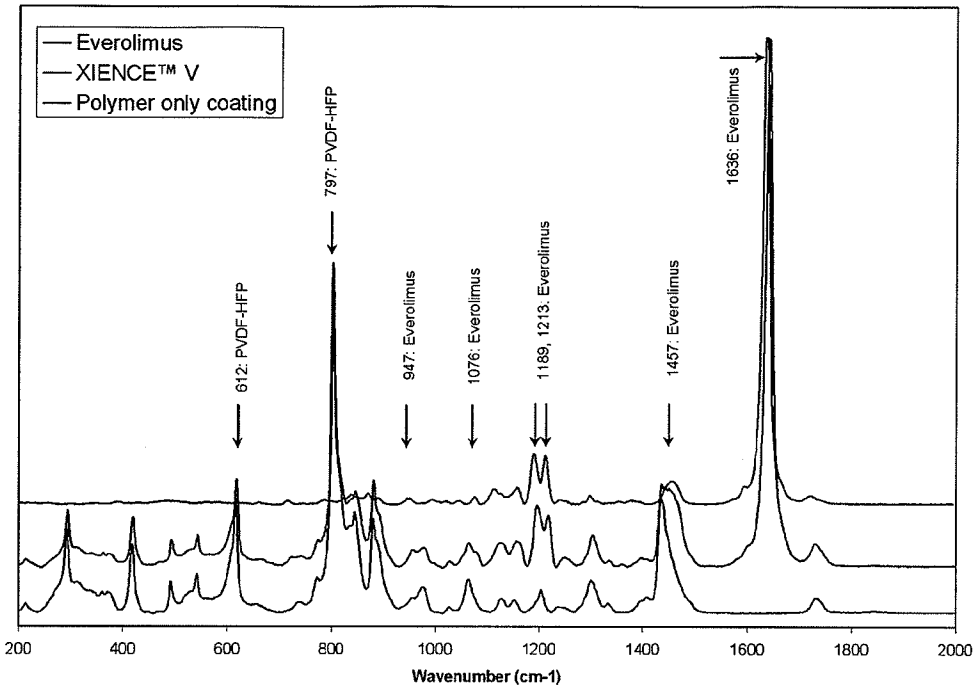

Figure 3.2.P.2–3 Polymer Coating, Drug Powder and XIENCE™ V

The PVDF-HFP peaks at 612 and 797 cm^{-1} (blue arrows) are specific to the crystalline phase and are not perturbed by the presence of the drug. Multiple everolimus specific peaks (red arrows) are clearly detected in the XIENCE™ V spectrum whether they overlap with polymer peaks or not.

The major everolimus peak, seen at 1636 cm^{-1}, is in a region of the spectrum without interference from the polymer excipients, and it does not exhibit a significant shift or change in shape when measured in the XIENCE™ V coating. Several smaller everolimus peaks (947, 1076, 1189, 1213 and 1457 cm^{-1}, red arrows) can also be seen in both the everolimus spectrum and in the XIENCE™ V spectrum where they overlap with polymer peaks.

In summary, all everolimus peaks are found in the XIENCE™ V spectrum, all peaks in the XIENCE™ V spectrum can be traced to the polymer excipients or the drug substance and no significant shifts are detected. This figure demonstrates that the drug is unperturbed by the PVDF-HFP copolymer or the coating process. It also indicates that the drug does not significantly impact the crystallization of PVDF-HFP. It is concluded from the Raman assessment that there are no new detectable impurities such as degradation products of the drug or the

polymer excipients in the XIENCE™ V stent within the detection limit of the test capability.

^{1}H NMR Spectroscopy

In addition to the GPC chromatogram assessment, ^{1}H NMR was performed on the following samples: everolimus drug powder, polymer excipient raw materials (PBMA and PVDF-HFP), and XIENCE™ V stents. The following ^{1}H NMR spectra were obtained with a Bruker 300 MHz spectrometer at room temperature using deuterated acetone as solvent.

The goal of this research study was to demonstrate that there is no interaction between the polymer excipients and the drug, in particular that the macrocycle and the triene structure of everolimus, are intact and have not bound to the polymer backbone.

Figure 3.2.P.2-4 shows that the specific peaks and peak structure of the two polymer excipients and the drug substance are exquisitely maintained in the XIENCE™ V product. The three methoxy peaks of the drug at 3.11, 3.26 and 3.40 ppm can clearly be seen in the XIENCE™ V spectrum, showing that these relatively sensitive moieties are maintained intact during the manufacturing of the XIENCE™ V product.

Another region of particular interest is between 5 and 6.5 ppm, where peaks of the triene protons can be found. Indeed these are two of the drug's most sensitive areas, since the triene is sensitive to oxidation and the macrocycle can be lost through hydrolysis followed by β-elimination.

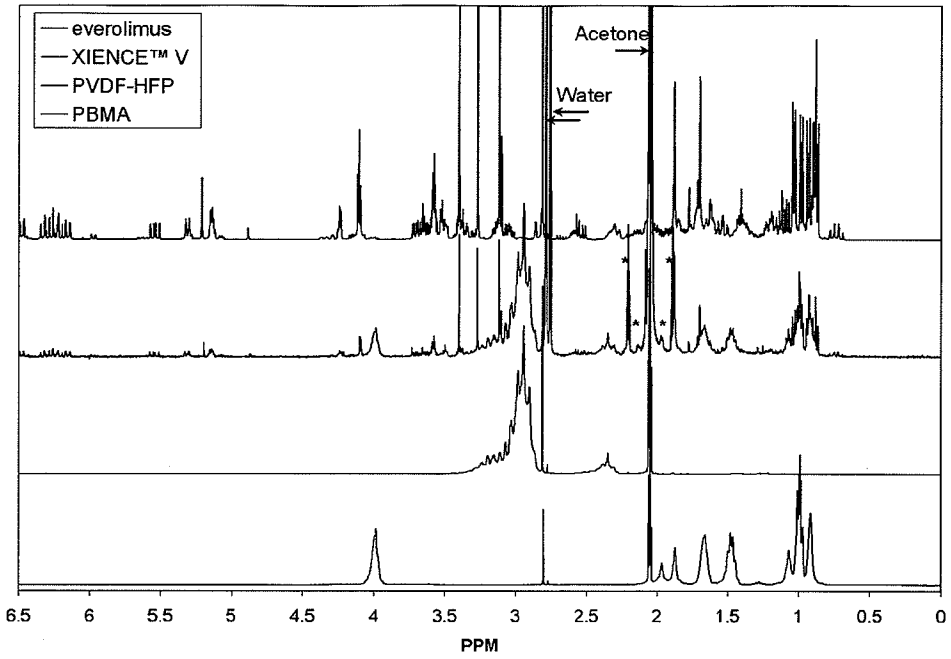

Figure 3.2.P.2–4 XIENCE™ V, Everolimus, PBMA and PVDF-HFP in Acetone-d_6

The water peak can be seen around 2.8 ppm, while the acetone residual peak is at 2.05 ppm with C_{13} satellites (*, 1.89, 1.97, 2.12 and 2.21 ppm), visible on the XIENCE™ V spectrum.

Figures 3.2.P.2-5 and 3.2.P.2-6 offer ^{1}H NMR spectra of different components of the XIENCE™ V stent. These magnified views highlight that the double bonds and macrocycle structure, as well as the methyl groups of everolimus, are maintained. The first graph highlights the area of the spectra where protons neighboring double bonds, or sp^2 protons, can be found. It is important to note that the relative intensity and the proton resonance of all peaks originating from the drug are reproduced in the XIENCE™ V spectrum. This indicates that the oxidation sensitive triene of the drug is intact following the manufacture of the XIENCE™ V product. Unsaturated protons are known to be very sensitive to the electronegativity of their immediate environment, therefore the lack of shift is a strong indication that the macrocycle is intact.[4] The second graph shows that the methyl groups of the drug compound can also be found in the XIENCE™ V spectrum, overlapping the $-CH_3$ protons from

[4] High-Resolution NMR Techniques in Organic Chemistry by Timothy D.W. Claridge, Oxford University Press, 1999

the PBMA. Although this region of the spectrum is fairly crowded, a more detailed analysis shows the presence of all the expected $-CH_3$ resonances and the lack of additional peaks. Taken together, these data confirm that there is no interaction between the drug and the polymer excipients.

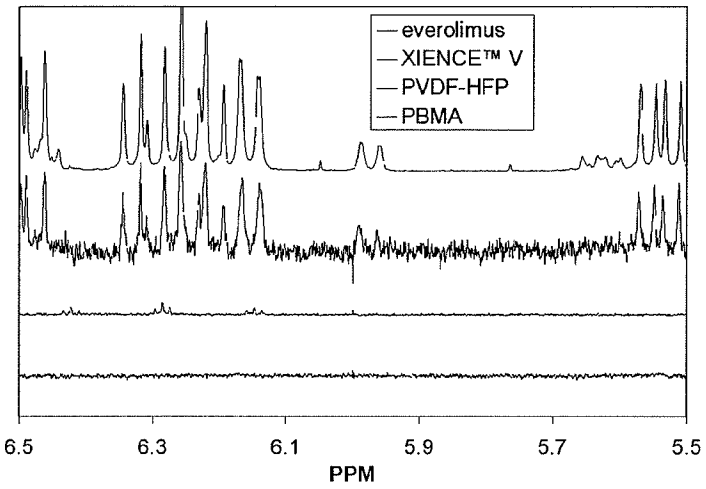

Figure 3.2.P.2-5 ^{1}H NMR Spectra, 5.0 to 6.5 ppm

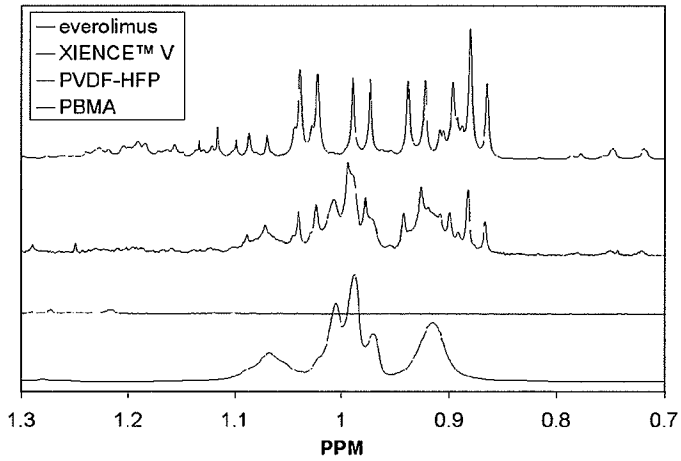

Figure 3.2.P.2-6 ^{1}H NMR Spectra, 0.7 to 1.3 ppm

In summary, these data support the conclusion that there is no chemical change of the drug structure during the XIENCE™ V formulation or coating process, and that there is no chemical interaction between the drug substance and the polymer excipients, PVDF-HFP and PBMA. As evidenced by three study data reported above, chemical interaction between the drug and the polymer does not occur during normal

manufacturing processes as well as under stressed conditions simulated by excessive sterilization cycles.

Solvent Screening and Selection
Organic solvents are used in the preparation of the spray coating solution. Solvents were screened based on the following considerations:

- Solubility of coating components
- Drug solubility and stability in solution
- Volatility
- Toxicity [5]
- Availability in high purity grade, preferably compendial where available
- Manufacturability.

In early screening studies, the composition of the spray solvent was found to have a significant impact on the coating quality as assessed by visual inspection. Rapidly evaporating solvents tended to prevent webbing between struts, but produced uneven coatings with a rough surface. Slower evaporating solvents provided better film forming properties and a smoother coating surface, but were found to result in a higher propensity for webbing and higher levels of residual solvent. The use of a combination of rapidly and slowly evaporating solvents in order to optimize coating quality is common practice in the spray paint industry. Similarly, stents coated with binary solvent systems showed better coating quality than those sprayed with single volatile solvents and lower residual solvent levels than stents coated with single, low-volatility solvents. For this reason, the use of binary solvent systems was further explored.

Everolimus and PBMA are soluble in a wide range of organic solvents, while PVDF-HFP dissolves best in solvents with a strong dipole moment, but medium to low hydrogen bonding (Solvay PVDF polymer brochure). Examples are ketones, and solvents like dimethylacetamide, dimethylformamide and dimethylsulfoxide. The latter three are powerful solvents that raised concerns about compatibility with processing equipment components in the manufacturing process. Cyclohexanone has relatively low volatility (boiling temperature = 155°C), and is a good solvent for all three major coating components (PBMA, PVDF-HFP and everolimus). A mixture of acetone and cyclohexanone (70/30 w/w) was found to have a good balance of volatility, and it produced smooth, uniform coatings with good adhesion, little webbing and low residual solvent levels.[6]

[5] ICH Harmonized Tripartite Guideline (Impurities: Guideline for Residual Solvents, July 17, 1997. Q3C, Guidance for Industry Q3C Impurities: Residual Solvents, December, 1997)

UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION

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CIRCULATORY SYSTEM DEVICES ADVISORY PANEL

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MEETING

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THURSDAY,
NOVEMBER 29, 2007

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The meeting convened at 8:00 a.m. at the Gaithersburg Holiday Inn, 2 Montgomery Village Avenue, Gaithersburg, Maryland, CLYDE W. YANCY, M.D., Acting Panel Chairperson, presiding.

PANEL MEMBERS PRESENT:

CLYDE YANCY, M.D, Acting Chairperson
RICHARD L. PAGE, M.D., Voting Member
JOHN C. SOMBERG, M.D., Voting Member
EUGENE H. BLACKSTONE, M.D., Consultant
JEFFREY A. BRINKER, M.D., Consultant
JOHN W. HIRSHFELD, M.D., Consultant
VALLUVAN JEEVANANDAM, M.D., Consultant
NORMAN S. KATO, M.D., Consultant
WARREN K. LASKEY, M.D., Consultant
DOUGLAS MORRISON, M.D., Consultant
SHARON-LISE NORMAND, Ph.D., Consultant
MARCIA S. YAROSS, Ph.D., Industry Representative
KAREN R. RUE, Consumer Representative

released by 30 days. And substantially all of the drug is eluted by 820 days.

XIENCE V coating design comprises a primer and matrix system. In the expanded view on the right, the stent strut is shown in white. The drug-carrying fluoropolymer matrix is shown in blue. And a thin primer layer is shown in red. It is the function of the primer to ensure good adhesion between the drug coating and the thin strut.

This system does not have a top coat. In our experience, this system allows for better manufacturing control and drug release than a top coat system for such thin coatings. This system also allowed us to optimize the adhesion of the coating to the stent strut while minimizing unwanted adhesions to the delivery balloon.

The drug-carrying matrix is an ultra pure copolymer comprised of vinylidene fluoride and hexafluoropropylene monomers. This polymer has been used in approved

cardiovascular, neurologic, and ophthalmic sutures.

The ratio of the vinylidene fluoride and hexafluoropropylene allows us to optimize the coating elasticity in order to prevent the coating from cracking upon stent expansion and coating toughness to ensure the durability of the coating during the act of stent delivery to the target lesion.

This polymer is one of the most stable entities chemically because of its durable carbon carbon backbone and the covalent carbon fluorene bonds. And this stability confers to this polymer a high degree of stability in vivo as well as biocompatibility. And, finally, this polymer has good hemocompatibility.

Shown here are micrographs of the XIENCE V system, illustrating its coating integrity. The coating was designed to minimize webbing, bridging, and strut-to-strut contact in the crimped state. It was also

designed to maintain the coating integrity after simulated use, stent expansion, and fatigue testing.

A key design objective for the XIENCE V system was to assure a level of hemocompatibility that was at least equivalent to the bare metal VISION platform. We tested hemocompatibility in accordance to ISO10-993 and showed in an un-hecronized ex vivo shunt study that the amount of polymers accumulated on the XIENCE V stent was less than that on the bare metal VISION stent. We, therefore, surpassed our objective of ensuring equivalent hemocompatibility to the bare metal stent.

We also studied the vascular response of the XIENCE V system and XIENCE V copolymer extensively in porcine models and demonstrated that all the way out to two years, the polymer response is equivalent to the VISION bare metal stent. We have also studied the vascular response of three times the amount of polymer on the stent and have

found the response equivalent to the bare metal vision stent.

So, in summary, the XIENCE V system is built on the proven VISION stent and stent delivery system. The VISION stent is flexible and has thin struts. It is also a deliverable stent.

We have also developed a thin, biocompatible drug coating that is effective at low drug loading. The polymer is stable. The coating is uniform and conformal around the stent struts.

The drug release is well-controlled and complete over time. And, finally, the system exhibits good hemocompatibility and vascular compatibility.

I will now turn over the podium to my preclinical colleague, Dr. Leslie Coleman.

DR. COLEMAN: Good morning. I would like to present to you an overview of the XIENCE V preclinical program. The clinical program consisted of an extensive

assessment of the biocompatibility of the XIENCE V system and assessment and characterization of the pharmacokinetics of XIENCE V, a comprehensive safety assessment, and an assessment of the endothelial cell response to XIENCE V.

The biocompatibility of the XIENCE V system was demonstrated through numerous in vitro and in vivo studies. All studies were conducted in compliance with applicable guidelines, and all studies passed.

The pharmacokinetics of the XIENCE V was characterized in a porcine coronary artery model. And, as you can see in the graph, the graph on the left demonstrates that the XIENCE V released everolimus in a consistent and controlled manner, with complete drug release by 120 days. And we believe that it's very important to have complete release of the drug from the system in order to allow for vessel healing.

These release kinetics translate

into effective arterial delivery, as you can see on the right graph, where we have controlled release of everolimus to the target tissue or the stented artery over time. This has allowed for the presence of everolimus during the first several months following stent implantation consistent with the peak cellular phases of neointimal hyperplasia.

The clinical pharmacokinetics of XIENCE V were studied in several substudies within the SPIRIT II and SPIRIT III clinical trials.

Results from all P-K substudies were consistent across geographies and showed limited systemic exposure of everolimus up to a total dose of 588 micrograms. And at all times the amount of systemic everolimus correlated with the number of stents implanted into the patient.

Importantly, systemic exposure to everolimus was well below the minimal therapeutic blood level of three nanograms per

enrolled and reviewed by data and safety monitoring boards without safety concerns.

This is an integrated, committed post-approval program that utilizes systematic high-quality science that will be delivered from a post-market research landscape. And this is very much in concert I think with all of our focus on what we need to guard the public health.

This program will prospectively provide progressively additional statistical certainty about the current directions of on-label XIENCE V safety as well as will prospectively provide new knowledge regarding off-label and real-world use of this device.

I will now turn the podium over to Krishna Sudhir from Abbott.

DR. SUDHIR: Thanks. Thank you, Mitch. Good morning. My name is Krishna Sudhir. I'm a cardiologist and Medical Director at Abbott Vascular. I will summarize the data that has been presented to you and

will leave you with a few concluding remarks.

Dr. Simhambhatla presented to you the overview of the XIENCE V design. It is built on the well-established VISION and MINI VISION stent and stent delivery system. It is a flexible stent with thin struts. And it has shown proven deliverability. It has a thin biocompatible drug coating. The polymer is durable and has been used in other medical and cardiovascular applications. The long-term biocompatibility is similar to a VISION bare metal stent. Everolimus, as pointed out by Gary Johnson, is a well-studied drug and, as such, is not a new molecular entity.

Dr. Coleman then presented to you an overview of the preclinical program. This is a comprehensive preclinical evaluation with 35 studies in 2 species, with study durations varying from 28 days to 2 years.

As shown in the scanning electron micrograph on the right, we presented evidence of rapid re-endothelialization, a smooth

muscle cell rich neointima with no persistent fibrin and minimal long-term inflammation. The hemocompatibility is comparable to a VISION bare metal stent. Thus, the preclinical safety profile is equivalent to a VISION bare metal stent.

You have seen our integrated pre-approval and post-approval clinical program with over 16,000 patients a few times during the last hour or so. Dr. Stone presented to you details of our pre-approval clinical data with the SPIRIT FIRST, SPIRIT II, and SPIRIT III clinical trials. In addition, Dr. Krucoff presented to you an overview of all the ongoing and planned clinical studies.

We have presented to you through Dr. Stone's presentation robust evidence of effectiveness. Consistent clinical and angiographic benefits of the XIENCE V stent have been shown compared to TAXUS in two consecutive randomized trials, SPIRIT II and